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Anal Dysplasia Screening and Treatment in a Southern Human Immunodeficiency Virus Clinic

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Abstract

Background—Persistent human papillomavirus infection in human immunodeficiency virus (HIV)-infected individuals has been strongly associated with anal squamous cell carcinoma. The incidence of anal squamous cell carcinoma continues to increase in this population despite advances in HIV therapy. There are few studies describing the prevalence of anal cancer precursors, treatment outcomes, and associated factors among HIV-infected populations in the southern United States.

Methods—A retrospective chart review was performed on 355 HIV-infected patients from a Southern HIV clinic who were 18 years or older and had received at least one anal Pap smear. Demographic and clinical variables were collected. Descriptive statistics, single variable, and multivariate logistic regression analysis were performed to evaluate for predictors of high-grade squamous intraepithelial lesion (HSIL). Odds ratios and 95% confidence intervals were constructed for independent measures.

Results—After the first anal Pap smear, 38.3% (70/183) of patients with abnormal results were lost to follow-up. Comparing patients with biopsy proven HSIL versus low-grade squamous intraepithelial lesions, patients were less likely to have HSIL if they had a higher CD4 count (odds ratio, 0.81; 95% confidence interval, 0.72–0.93; $P = 0.0022$). Treatment success after the first round of treatment for topical and infrared coagulation therapy was 36.7% (18/49, all therapy types), and of those who achieved biopsy proven treatment success at follow-up screening, 94.4% (17/18) required subsequent therapy.

Conclusions—Patients with a higher CD4 count were less likely to have HSIL. CD4 nadir, number of sexual partners, and race/ethnicity were not significantly associated with the presence of HSIL.

Among men who have sex with men (MSM), the incidence of anal carcinoma is approximately 35 cases per 100,000 population, and rates of anal cancer in human immunodeficiency virus (HIV)-positive MSM approach 128/100,000 population in some studies, likely representing human papillomavirus (HPV) and HIV coinfection.[1–5]

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Based on the cervical cancer screening paradigm, anal Pap smears (APS) have been used in some settings. Essentially all of the anal Pap smear performance and outcomes research has been derived from patient populations outside the southern United States. Important cultural, behavioral, and genetic differences exist between patients served in the study clinic, which has larger minority representation than previous study populations. It is unclear how these differences contribute to the natural history of HPV-mediated anal SIL and progression to carcinoma in these populations. This study represents a first step in the process to define the natural history of HPV-mediated anal SIL in a southern clinic population.

METHODS

Clinic Organization

The study institution implemented yearly APS testing in HIV-infected MSM as part of routine clinical care. Results of APSs graded atypical cells of undetermined significance (ASCUS) or higher prompted referral to the high-resolution anoscopy (HRA) clinic. If high-grade squamous intraepithelial lesion (HSIL) was confirmed via biopsy, treatment was pursued through three possible modalities: imiquimod (5%) or 5-fluorouracil (5-FU) cream applied intra-anally for up to 16 weeks or HRA-directed infrared coagulation therapy (IRC).

Study Organization

A retrospective chart review was performed on 355 HIV-positive patients from a North Carolina-based HIV clinic who were 18 years or older and had received at least 1 APS between January 1, 2008, and August 31, 2013. Multiple demographic and disease-related data were collected. Subsequent encounters after the initial HRA were reviewed for lesion regression after treatment. CD4 and HIV viral load values were taken as the values in closest proximity to either the HRA or APS dates of interest. A suppressed viral load was defined as <200 copies/mL. The HSIL via biopsy was defined as any anal intraepithelial neoplasia (AIN2) or higher (regardless of P16 status as the Lower Anogenital Squamous Terminology Consensus had not been fully adopted in our pathology group).[6] The APS cytology results of ASCUS or higher were considered abnormal. Treatment success by biopsy (after either 5-FU/Imiquimod/IRC) was defined as regression from AIN2 or higher (this includes AIN2 regardless of P16 status and AINIII/CIS, as the higher values) to AIN1 or lower. Treatment failure was defined as follow-up HRA with biopsy showing continued the presence of AIN2 or higher.

Statistical Analysis

There were only 7 women in the study, and they were excluded from the statistical analysis. Findings from the first APS were evaluated, and for those with abnormal results, rates of follow-up for HRA evaluation were analyzed using Fisher exact test.

Continuous variables were described using means and standard deviations, whereas categorical variables were described using counts and proportions. For each first HRA evaluation and biopsy, patients with HSIL and low-grade squamous intraepithelial lesion (LSIL) were compared to ascertain if various factors (CD4 count, CD4 nadir, and so on) were associated with HSIL or LSIL. Differences in continuous variables were compared

using Kruskal-Wallis tests and differences in categorical variables were compared using Fisher exact tests.

In patients, who completed an HRA, were referred to treatment, completed treatment, and had a follow-up HRA, we compared various dichotomous HRA outcomes from the patient's first diagnostic HRA to the patient's post-therapeutic follow-up HRA using Fisher exact tests. Outcomes included treatment failure versus treatment success, as defined above, stratified by treatment modality.

Logistic regression analysis was performed on those who were found to have HSIL on their first HRA to predict treatment failures. Models were adjusted for race, current smoking, whether patients were actively on antiretroviral therapy (ART), CD4 value, number of years since HIV diagnosis, and suppressed viral load. Odds ratios (OR) and 95% confidence intervals (CIs) were constructed for single and multivariable models.

All analyses were performed in SAS 9.4 (Cary, NC), and all hypothesis testing was two sided at the 0.05 significance level.

RESULTS

Study Participants

Of the 355 patient charts reviewed, 348 (98.0%) were men, and of this group, 318 (91.4%) were MSM (Table 1). The median age was 42 (18–75), the majority of patients were black (60%) or white (33.3%), and almost half (45.9%) reported a smoking history before their first APS.

Anal Pap Smear Follow-Up Outcomes

Over two thirds of the study population (N = 253 [71.2%]) had an abnormal APS. Twenty-eight percent (71/253) of all patients who were found to have ASCUS or higher on the initial APS failed to follow-up for HRA despite attempts at scheduling these visits (Table 2). When this cohort is further subdivided by ethnic groups (Table 2), African American males were less likely than white males to follow-up for an HRA procedure (65.4% vs 83.3%, respectively, $P = 0.002$). Of the 182 individuals who had a follow-up HRA, 75 (41.2%) were found to have only LSIL, and 107 (58.8%) were found to have HSIL.

Factors Predicting Presence of HSIL

When comparing all patients who were diagnosed with HSIL and LSIL by HRA-guided biopsy (Table 3), we found that individuals with higher CD4 counts were less likely to have HSIL (OR, 0.81; 95% CI, 0.72–0.93; $P = 0.0022$). It should be noted that the mean time between CD4 and viral load testing and HRA was 2.3 months. Although not significant, having a suppressed viral load was found to approach statistical significance as a factor that was protective against HSIL (OR, 0.54; 95% CI, 0.26–1.11; $P = 0.094$), and being a cigarette smoker was found to approach statistical significance as well (OR, 1.59; 95% CI, 0.89–2.94; $P = 0.13$) as a factor that increased the odds of having HSIL. CD4 nadir, number of lifetime sexual partners, African American race, white race, and number of years since diagnosis with HIV were not found to significantly impact the odds of developing HSIL.

In the multivariate logistic regression analysis of individuals predicting HSIL on the first HRA (Table 4), increased CD4 values were associated with decreased odds of HSIL (OR, 0.82; 95% CI, 0.68–0.97; $P = 0.022$). Cigarette smoking approached statistical significance with increased odds of developing HSIL (OR, 1.72, 95% CI, 0.89–3.32; $P = 0.11$).

Treatment Outcomes

Topical therapy (5-FU or imiquimod (5%) creams) or IRC was offered to patients based on the location and extent of HSIL found on HRA biopsies. Among those who underwent a follow-up HRA posttreatment (N = 49/94), treatment success for all therapies combined was 36.7% (18/49). With regard to IRC, 61.1% (22/36) of patients treated required repeat therapy compared to 69.2% (9/13) of those treated with 5-FU or imiquimod.

DISCUSSION

Patients with a higher CD4 count before HRA-guided biopsy were found to be less likely to have HSIL, suggesting a protective effect. In contrast to past studies, no statistically significant effect was found from CD4 nadir, number of sexual partners, length of time infected with HIV, or race/ethnicity on rates of biopsy-proven HSIL.[7–11] A nonstatistically significant trend was found for individuals with suppressed viral load on the single variable analysis (Table 3) to have a reduced odds of having HSIL (OR, 0.54; 95% CI, 0.26–1.11; $P = 0.094$), which would have been consistent with prior data.[12] Additionally, cigarette smoking was found to have a nonstatistically significant trend toward increased odds of developing HSIL in both the single variable and multivariable logistic regression analysis of the data (Tables 3 and 4), and this was consistent with prior literature.[7]

The study data echoes prior studies showing that treatment modalities were often suboptimal in the short term.[13] In this population, IRC was found to have a treatment failure rate of 61.1% (22/34) after 1 treatment, and this was consistent with previous results.[14] The topical treatments had the lowest rate of treatment success after the first round of therapy at only 30.8% (4/13) which was consistent with prior data.[15] Both the imiquimod and 5-fluorouracil therapies require multiple weeks of digital intra-anal application of the creams, and there is no way to control for administration. Also, these medications were used for diffuse high-grade AIN, whereas IRC was used for more limited disease. With regard to the IRC therapies, regions which were biopsied previously and found to have HSIL were treated, and on the follow-up HRA, these areas were preferentially biopsied again to assure pathological disease regression. Overall, the relatively high rate of recurrence of HSIL may be partially mediated by the presence of metachronous lesions.[16–18]

Limitations of this study include the retrospective nature of the study and the high rates of loss to follow-up (28%), which was most marked among African American participants (35%). Unfortunately, the sexual partner data was not collected routinely until after September 28, 2012. Although this study's sample size is comparable to or greater than past studies, it remains a relatively small group of patients. Many questions remain regarding the natural history of HPV-induced anal SIL, the effectiveness of the APS screening process, and the long-term efficacy of present treatment modalities.

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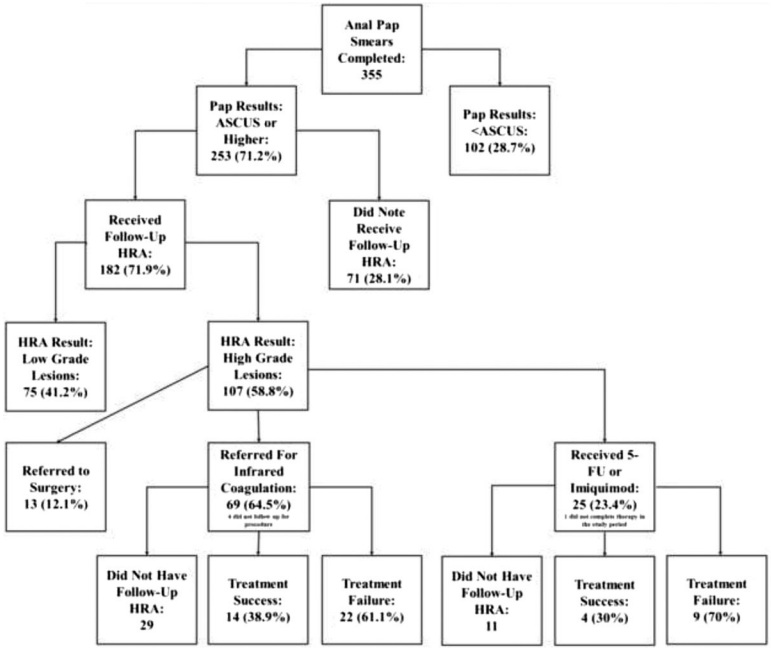

Figure.
Breakdown of results.

TABLE 1

Study Population Demographics

	Males	Females
Total	348	8
Age: median (range), y	42(18–75)	42.5
Age: mean (SD)	40.5 (11.7)	41.8
Race		
African American (%)	209 (60.1)	7 (87.5)
White (not Hispanic) (%)	116 (33.3)	1 (12.5)
White (Hispanic) (%)	17 (4.9)	0 (0)
Asian (%)	3 (0.9)	0 (0)
American Indian/Alaska Native (%)	2 (0.6)	0 (0)
Multiracial (%)	1 (0.29)	0 (0)
Sexual behavior		
Men who have sex with men (%)	318 (91.4)	N/A
Men who have sex with men and women (%)	15 (4.3)	N/A
Men who have sex with women (%)	15 (4.3)	N/A
Women who have sex with men (%)	N/A	6 (75)
Women who have sex with women (%)	N/A	1 (12.5)
Women who have sex with men and women (%)	N/A	1 (12.5)
Other		
Smokers before first anal pap smear (%)	157 (45.9)	3 (37.5)

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TABLE 2

Anal Pap Smear Follow-Up Stratified by Pap Smear Result

Results of APS	**Number (%) Who Did Not Have Subsequent HRA**	**Number (%) Who Had Subsequent HRA**
ASCUS (N = 126)	44 (34.9%)	82 (65.1%)
LSIL (N = 110)	23 (20.9%)	87 (79.1%)
ASCUS-H (N = 12)	3 (25.0%)	9 (75.0%)
HSIL/Carcinoma in situ (N = 5)	1 (20.0%)	4 (80.0%)
Carcinoma (N = 0)	0	0
Total Number (N = 253)	71 (28.1%)	182 (71.9%)

Anal Pap smear results stratified by age

	Age, y					
	18–25	26–35	36–45	45–55	56–65	65+
ASCUS (N = 126)	11	38	26	38	11	2
LSIL (N = 110)	14	42	25	22	7	0
ASCUS-H (N = 12)	3	3	0	5	1	0
HSIL/Carcinoma in situ (N = 5)	1	1	1	0	2	0
Carcinoma (N = 0)	0	0	0	0	0	0

Follow-Up from First Anal Pap Smear (With ASCUS or Higher) Stratified by Race

Race	Number (%) Who Did Not Have Subsequent HRA	Number (%) Who Had Subsequent HRA
African American	53 (34.6%)	100 (65.4%)
White	16 (16.7%)	80 (83.3%)

TABLE 3

Risk Factors for HSIL at First HRA Single-Variable Analysis

Category	OR	95% CI	*P*
Race (AA to white, not Hispanic)	1.06	(0.58–1.95)	0.85
No. years since HIV diagnosis	0.97 *	(0.78–1.19)	0.75
Age, y	0.90 *	(0.79–1.03)	0.12
Mean CD4 value	0.81 †	(0.72–0.93)	0.0022
Mean CD4 nadir	0.90 †	(0.79–1.03)	0.13
On ART	1.51	(0.61–3.85)	0.37
Suppressed viral load	0.54	(0.26–1.11)	0.094
Cigarette smokers	1.59	(0.89–2.94)	0.13
Lifetime partners >11	0.68	(0.29–1.60)	0.38

* Odds ratio per 5 year increase.

† Odds ratio per 100 unit increase.

TABLE 4

Predicting High-Grade Dysplasia Using Multivariate Logistic Regression Analysis on HRA 1

Category	OR	95% CI	*P*
Race (AA to white, not Hispanic)	1.29	(0.66–2.52)	0.45
No. years since HIV diagnosis	1.16 *	(0.88–1.53)	0.29
Age, y	0.88 *	(0.74–1.05)	0.17
Mean CD4 value	0.82 †	(0.68–0.97)	0.022
Mean CD4 nadir	0.99 †	(0.82–1.21)	0.97
On ART	1.11	(0.31–4.05)	0.87
Suppressed viral load	0.87	(0.34–2.22)	0.78
Cigarette smokers	1.72	(0.89–3.32)	0.11

* OR per 5 year increase.

† OR per 100 unit increase.